# PCA001 Statistical Analysis Plan v1.0, 31Oct2024

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**Official Title:**

A Phase 1/Phase 2 Trial to Evaluate Safety, Immunogenicity and PSA Response of VTP-850 Prostate Cancer Immunotherapeutic in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer

**NCT Number:**

NCT05617040

**Document Date:**

31 October 2024

# Statistical Analysis Plan

**A Phase 1/Phase 2 Trial to Evaluate Safety, Immunogenicity and PSA Response of VTP-850 Prostate Cancer Immunotherapeutic in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer**

Statistical Analysis Plan: Final
Statistical Analysis Plan: 1.0
Statistical Analysis Plan Date: 31-October-2024

Investigational Product: VTP-850 (ChAdOx1-PCAQ and MVA-PCAQ)

Protocol Reference: PCA001
Fortrea Study ID: 000000235934
Sponsor: Barinthus Biotherapeutics (UK) Ltd.

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## Glossary of Abbreviations

| Abbreviation | Term |
|---|---|
| ADT | Androgen deprivation therapy |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| BRCA | Breast Cancer gene |
| ChAdOx1 | Chimpanzee adenovirus Oxford 1 |
| CI | Confidence Interval |
| COVID-19 | Coronavirus Disease of 2019 |
| CRF | Case Report Form |
| CT | Computed tomography |
| DBP | Diastolic BP |
| DLT | Dose Limiting Toxicity |
| ECG | Electrocardiogram |
| EES | Efficacy Evaluable Set |
| ELISpot | Enzyme linked immunospot assay |
| FAS | Full Analysis Set |
| ICF | Informed consent form |
| IM | Intramuscular(ly) |
| IV | Intravenous(ly) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFS | Metastasis-free survival |
| MRI | Magnetic resonance imaging |
| MSI-H | Microsatellite Instability-High status |
| MVA | Modified Vaccinia virus Ankara |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for AEs |
| PAP | Prostatic Acid Phosphatase |
| PBMC | Peripheral Blood Mononuclear Cells |
| PCAQ | Prostate Cancer Quadrivalent |
| PCI | Potentially Clinically Important |
| PCWG-3 | Prostate Cancer Working Group 3 |
| PPS | Per-Protocol Set |
| PSA | Prostate-specific antigen |
| PSMA | Prostate-specific membrane antigen |
| PT | Preferred Term |
| QTcF | Fridericia corrected QT interval |
| RP2R | Recommended Phase 2 regimen |
| SAE | Serious AE |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SI | International System of Units |
| SOC | System Organ Class |
| STEAP1 | Six-transmembrane epithelial antigen of prostate 1 |
| TBC | To Be Confirmed |

| Abbreviation | Term |
|---|---|
| TEAE | Treatment Emergent AEs |
| TFLs | Tables, Figures and Listings |
| TTM | Time to Metastasis |
| WHO DD | World Health Organization Drug Dictionary |

## 1. Source Documents

The SAP was written based on the following documentation:

| Document | Date | Version |
|---|---|---|
| Protocol | 18-Apr-2024 | 5.0 |
| eCRF | 30-May-2024 | 3.16 |

# 2. Protocol Details

## 2.1. Overall Study Design

This is a multicentre, Phase 1/2, open-label clinical trial of the VTP-850 prime-boost immunotherapeutic in men with biochemical recurrence after definitive local therapy for prostate cancer.

Participants in all cohorts will receive the ChAdOx1-PCAQ component on Day 1 (prime) and the MVA-PCAQ component on Days 29 and 57 (boosts; Intervention Period). Participants will be followed until the Month 6 Visit or start of new therapy such as ADT or until development of unequivocal metastatic prostate cancer (Short-term Follow-up Period). Participants who have a PSA response will be followed for an additional 18 months, up to 24 months from first dose, or until start of new therapy such as ADT or development of unequivocal metastatic prostate cancer (Long-term Follow-up Period). In the event that a participant experiences a confirmed PSA response but subsequently experiences PSA progression more than 2 months after their final dose of VTP-850, an additional dose of MVA-PCAQ may be offered to the participant if the investigator believes it may be in the participant's best interest, after discussion with the medical monitor and agreement of the SMC.

Phase 1 will determine the recommended Phase 2 regimen (RP2R; the dose level of both ChAdOx1-PCAQ and MVA-PCAQ and the route of administration of MVA-PCAQ) that will be used in Phase 2 and will follow a 3+3 design.

The first 3 participants will be enrolled in Cohort 1. Enrolment of the first 3 participants in each cohort will be staggered by at least 9 days. The medical monitor will review the safety data for the previous participant, at least 7 days after the prime dose and after the first booster dose of VTP-850, before the corresponding dose is administered to the next participant. The safety review will include data from at least 7 days after each ChAdOx-PCAQ prime dose; at least 7 days after the first booster MVA-PCAQ dose if administered intramuscularly (IM); and at least 14 days after the first booster dose of MVA-PCAQ if administered intravenously (IV). If 1 or more of the 3 participants has a dose limiting toxicity (DLT), 3 additional participants may be enrolled into Cohort 1. If there is no DLT after the first dose of VTP-850 in the first 3 participants, 3 participants will be enrolled into each of Cohorts 2 and 3 concurrently, with the first participants in Cohorts 2 and 3 staggered by at least 9 days to allow for medical review. If DLT is not seen in more than 1 participant in Cohort 2 after the first dose of VTP-850, then an additional 3 participants will be enrolled into Cohort 2. Safety data for the DLT period following each booster dose will be assessed by the medical monitor prior to the corresponding booster dose being administered to additional participants. If DLT is not seen after the first dose of VTP-850 in more than 1 participant in Cohort 3 then an additional 3 participants will be enrolled into Cohort 3. Safety data for the DLT period following each booster dose will be assessed by the medical monitor prior to the corresponding booster dose being administered to additional participants.

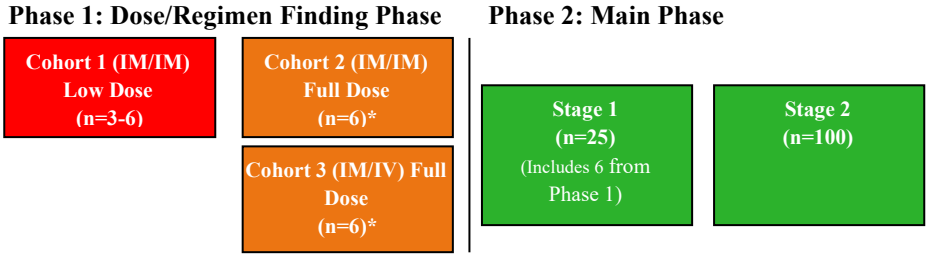
Phase 1 is designed with dosing of MVA-PCAQ on Days 29 and 57 for 6 participants each in Cohorts 2 and 3. In November 2023, Barinthus paused enrollment and dosing in PCA001 following an unwitnessed death in a Cohort 3 participant between the 1st MVA dose and the planned 2nd dose. At the time of the pause, only 4 participants in Cohorts 2 and 3 had received the full treatment course of ChAdOx1 and two MVA doses. Participants who withdraw before beginning dosing, before completion of all planned dosing or who have delays in dosing will be replaced (unless the reason for not completing dosing per protocol is related to a stopping rule criteria). Because of this, an additional 8 participants will be enrolled and treated in Phase 1 to provide a full complement of 6 fully treated participants in Cohorts 2 and 3.

If the safety of one or more cohorts in Phase 1 is acceptable after all participants have been followed through the DLT period after the first booster dose of VTP-850, then a Phase 2 dosing regimen will be selected based on safety data, and recruitment to Phase 2 will be opened.

Phase 2 of the trial will consist of 2 sequential stages.

In Stage 1 of Phase 2, 19 additional participants will be enrolled at the chosen Phase 2 regimen. If 4 or more of the 25 participants at the RP2R (out of the 19 Phase 2 participants and the 6 Phase 1 participants who received the same dose regimen according to the dosing schedule) have a PSA response, Stage 2 will be opened to enrolment of up to 100 additional participants. If 3 or fewer of the 25 participants have a PSA response in Stage 1, no further participants will be enrolled. PSA response is defined as ≥50% reduction in serum PSA compared to baseline at any time, measured at two consecutive timepoints, at least 2 weeks apart.

The Safety Monitoring Committee (SMC) will make a recommendation whether 1) to enrol each cohort in Phase 1, 2) about the choice of RP2R after reviewing available safety data and 3) to open enrolment in Phase 2 Stage 2 after reviewing available safety and efficacy data after at least 4 participants have exhibited a PSA response.




Abbreviations: IM=intramuscular, IV=intravenous, *n=number of participants who have received their scheduled doses of MVA-PCAQ on Day 29 and Day 57

This SAP will cover the analyses for the Phase 1 part of the study. Phase 2 has not commenced and therefore any analyses related to or more applicable to the phase 2 part of the study are not covered in this SAP. A separate SAP will be written to cover the phase 2 part of the study in future.

## 2.2. Study Objectives

### 2.2.1. Primary Objective(s)

To evaluate the safety of VTP-850 prime-boost regimens, with the booster dose administered either IM or IV, and to establish an RP2R.

#### 2.2.1.1. Endpoints for the Primary Objective(s)

- Number and proportion of participants with AEs, treatment-related AEs, ≥Grade 3 AEs, ≥Grade 3 treatment-related AEs, serious adverse events, and treatment-related serious adverse events
- Number and proportion of participants with clinically significant laboratory values
- Change from baseline for laboratory tests, electrocardiogram and vital sign measurements at each time point of collection

Full details for each endpoint are provided in Section 6.7.

### 2.2.2. Secondary Objective(s)

- To evaluate the PSA response rate to VTP-850
- To evaluate the durable PSA response rate to VTP-850

The following objectives are only applicable to the phase 2 of the study, and therefore will not be addressed in this phase 1 SAP:

- To evaluate the duration of PSA response to VTP-850 (for the subset of participants with PSA response)
- To assess the metastasis-free survival (MFS) and time to metastases (TTM) of the subset of participants with PSA response
- To assess the time to start of ADT for the participants with PSA response

#### 2.2.2.1. Endpoints for the Secondary Objective(s)

The following are the relevant endpoints corresponding to the secondary objectives in the phase 1 part of this study:

- Percentage of participants with ≥50% reduction in serum PSA compared to baseline at any time, based on two consecutive measurements at least 2 weeks apart
- Percentage of participants with confirmed PSA response compared to baseline without having PSA progression on or before Month 8

Full details for each endpoint are provided in Section 6.6.2.

### 2.2.3. Exploratory Objective(s)

- To characterise immunogenicity (including antigen-specific T-cell magnitude, phenotype and functionality associated with each regimen)

The following objectives are only applicable to the phase 2 of the study, and therefore will not be addressed in this phase 1 SAP:

- To explore association of PSA response with biomarkers
- To look for evidence of resolution of lesions on prostate-specific membrane antigen (PSMA) scan after administration of VTP-850 (if documented at baseline), and association of resolution of such lesions with PSA response in the subset of participants with baseline PSMA scan who have a PSA response on trial
- To assess the MFS and TTM of all participants

#### 2.2.3.1. Endpoints for the Exploratory Objective(s)

The following are the relevant endpoints corresponding to the exploratory objectives in the phase 1 part of this study:

- CD4+ and CD8+ T-cell response to the VTP-850 antigens in the peripheral blood as measured by multi-parameter flow cytometry and enzyme linked immunospot assays (ELISpot)

Full details for each endpoint are provided in Section 6.6.4.

## 2.3. Sample Size and Power

A total of approximately 144 participants will be enrolled. Approximately 25 participants will be enrolled into the Phase 1 of the study. A sample size of approximately 125 participants will be eligible for inclusion in the Phase 2 efficacy evaluation. Full details of the sample size calculation are provided in the protocol Section 11.4.

## 2.4. Primary Efficacy Variable(s)

Not Applicable.

## 2.5. Secondary Efficacy Variable(s)

Prostate-specific antigen (PSA) is measured using blood samples for high-sensitivity serum PSA and is assessed at the central laboratory. Samples are collected at Screening, baseline (Day 1), Day 29, 57, 64, 91 and then in monthly intervals from Months 4 to 12 and then every 2 months to Month 24. Measurements from Months 7 to 24 are only made if a participant has a PSA response within the first 6 months and only until the start of new therapy such as ADT or development of unequivocal metastatic prostate cancer. Baseline PSA is defined using the

rules for baseline specified in Section 5.1.2. PSA response and progression are defined in Section 6.6.2. Missing values will not be imputed.

## 2.6. Exploratory Efficacy Variable(s)

### 2.6.1. Intracellular Cytokine Staining

Prostate cancer-specific CD4+ and CD8+ T cell subsets will be further defined by phenotypic markers of activation, differentiation, memory and functionality using multiparameter flow cytometry assays such as intracellular cytokine staining (ICS). Immunogenicity endpoints analyzed by Barinthus Bio's Immunology laboratory will be evaluated from PBMC samples at Days 1, 29, 36, 57, 64, 91 and Months 8 and 12. Participants who receive an optional third MVA dose or whose second MVA dose is delayed because of the study pause will have additional PBMC samples collected after this last MVA dose.

For the ICS data, the general class of endpoints is the background-subtracted (i.e., DMSO-subtracted) percentage of CD4+ or CD8+ T-cells that positively express at least one of four cytokines (as described in Table 2). For CD4+ cells, the four cytokines of interest are CD154, IFNg, TNFa, and IL-2. For CD8+, the four cytokines of interest are CD107a, IFNg, TNFa, and IL-2 (i.e., IFNg, TNFa, and IL-2 are common cytokines of interest for CD4+ and CD8+ cells).

Cytokine expression in CD4+ and CD8+ cells will be assessed for four stimulation antigens: PSA, PAP, 5T4, STEAP1. Hence, for each timepoint for a participant, the ICS data will include 4 records of interest, one for each of the 4 stimulation antigens[1].

Background-subtracted percentages of positive cytokine expression are calculated as follows:

1. For each sample's four stimulation antigens (i.e., PSA, PAP, 5T4, STEAP1), calculate the percentage of CD4+ or CD8+ cells with total positive cytokine expression (i.e. all combinations in Table 2) by dividing the cell count with positive expression by the respective total CD4+ or CD8+ count for the sample.
2. Likewise, calculate the background percentage of CD4+ or CD8+ cells with positive expression using the same method and the sample's DMSO record.
3. The background-subtracted percentage with positive cytokine expression is the subtraction of the background percentage expression calculated in Step 2 from the percentage calculated in Step 1. If the background expression is greater than the stimulation antigen's expression, the percentage with positive expression for the stimulation antigen should be set to 0.

[1] In addition to records for the 4 stimulation antigens of interest, the ICS data also include 3 additional stimulation records at each timepoint. CMV is an antigen-specific T cell response positive control, PMA is an assay positive control, and DMSO is the background/negative control. For analysis, the CMV and PMA stimulations can be ignored. The DMSO stimulation is used to determine the background-subtracted count of positively expressed CD4+ or CD8+ cells for each cytokine as noted above.

For example, calculation of the percentage of CD4+ cells with positive expression of all 4 CD4+ cytokines of interest (i.e., CD154, IFNg, TNFa, and IL-2) for the 5T4 antigen would be as follows using the hypothetical data below:

| Participant ID | Timepoint | Stimulation | CD4 count | CD4/107+154+IFNg+IL2+TNFa+ | CD4/107-154+IFNg+IL2+TNFa+ |
|---|---|---|---|---|---|
| 1 | Day 29 | DMSO | 101599 | 3 | 16 |
| 1 | Day 29 | PSA | 103404 | 0 | 5 |
| 1 | Day 29 | PAP | 103093 | 0 | 1 |
| 1 | Day 29 | 5T4 | 103111 | 461 | 6316 |
| 1 | Day 29 | STEAP1 | 106261 | 0 | 0 |
| 1 | Day 29 | CMV | 108116 | 0 | 0 |
| 1 | Day 29 | PMA | 91592 | 0 | 4 |

1. For 5T4, the count of CD4+ cells that positively express CD154, IFNg, TNFa, and IL-2 is:
   461 (i.e., the CD4+ cells that also express CD107) +
   6316 (i.e., the CD4+ cells expressing the 4 cytokines of interest without CD107) = 6777

   The percentage of CD4+ cells expressing all 4 cytokines is therefore:
   (6777/103111) × 100 = 6.573%
2. For DMSO, the equivalent background count of cells expressing all 4 cytokines is 3 + 16 = 19.

   Expressing this as a background percentage of expression is calculated as:
   (19/101599) × 100 = 0.019%
3. Hence, the background-subtracted percentage with positive expression of all 4 cytokines for the 5T4 antigen is 6.573-0.019 = 6.554%

For each T cell, 15 cytokine combinations (Table 1) per stimulation antigen will be calculated for summarization using the approach documented above. Note that the all-negative response categorization, where no cytokine is expressed, does not need to be calculated.

**Table 1: ICS Cytokine Response Combinations**

| T Cell | Cytokines (%) | Cytokine combination naming |
|---|---|---|
| CD4+ | CD4/CD107a+CD154+IFNg+IL2+TNFa+<br>CD4/CD107a-CD154+IFNg+IL2+TNFa+ | IFNg+ / IL2+ / TNFa+ / CD154+ |
| | CD4/CD107a+CD154-IFNg+IL2+TNFa+<br>CD4/CD107a-CD154-IFNg+IL2+TNFa+ | IFNg+ / IL2+ / TNFa+ / CD154- |
| | CD4/CD107a+CD154+IFNg+IL2+TNFa-<br>CD4/CD107a-CD154+IFNg+IL2+TNFa- | IFNg+ / IL2+ / TNFa- / CD154+ |
| | CD4/CD107a+CD154-IFNg+IL2+TNFa-<br>CD4/CD107a-CD154-IFNg+IL2+TNFa- | IFNg+ / IL2+ / TNFa- / CD154- |
| | CD4/CD107a+CD154+IFNg+IL2-TNFa+<br>CD4/CD107a-CD154+IFNg+IL2-TNFa+ | IFNg+ / IL2- / TNFa+ / CD154+ |
| | CD4/CD107a+CD154-IFNg+IL2-TNFa+<br>CD4/CD107a-CD154-IFNg+IL2-TNFa+ | IFNg+ / IL2- / TNFa+ / CD154- |
| | CD4/CD107a+CD154+IFNg+IL2-TNFa-<br>CD4/CD107a-CD154+IFNg+IL2-TNFa- | IFNg+ / IL2- / TNFa- / CD154+ |
| | CD4/CD107a+CD154-IFNg+IL2-TNFa-<br>CD4/CD107a-CD154-IFNg+IL2-TNFa- | IFNg+ / IL2- / TNFa- / CD154- |
| | CD4/CD107a+CD154+IFNg-IL2+TNFa+<br>CD4/CD107a-CD154+IFNg-IL2+TNFa+ | IFNg- / IL2+ / TNFa+ / CD154+ |
| | CD4/CD107a+CD154-IFNg-IL2+TNFa+<br>CD4/CD107a-CD154-IFNg-IL2+TNFa+ | IFNg- / IL2+ / TNFa+ / CD154- |
| | CD4/CD107a+CD154+IFNg-IL2+TNFa-<br>CD4/CD107a-CD154+IFNg-IL2+TNFa- | IFNg- / IL2+ / TNFa- / CD154+ |
| | CD4/CD107a+CD154-IFNg-IL2+TNFa-<br>CD4/CD107a-CD154-IFNg-IL2+TNFa- | IFNg- / IL2+ / TNFa- / CD154- |
| | CD4/CD107a+CD154+IFNg-IL2-TNFa+<br>CD4/CD107a-CD154+IFNg-IL2-TNFa+ | IFNg- / IL2- / TNFa+ / CD154+ |
| | CD4/CD107a+CD154-IFNg-IL2-TNFa+<br>CD4/CD107a-CD154-IFNg-IL2-TNFa+ | IFNg- / IL2- / TNFa+ / CD154- |

| T Cell | Cytokines (%) | Cytokine combination naming |
|---|---|---|
| | CD4/CD107a+CD154+IFNg-IL2-TNFa-<br>CD4/CD107a-CD154+IFNg-IL2-TNFa- | IFNg- / IL2- / TNFa- / CD154+ |
| CD8+ | CD8/CD107a+CD154+IFNg+IL2+TNFa+<br>CD8/CD107a+CD154-IFNg+IL2+TNFa+ | IFNg+ / IL2+ / TNFa+ / CD107+ |
| | CD8/CD107a-CD154+IFNg+IL2+TNFa+<br>CD8/CD107a-CD154-IFNg+IL2+TNFa+ | IFNg+ / IL2+ / TNFa+ / CD107- |
| | CD8/CD107a+CD154+IFNg+IL2+TNFa-<br>CD8/CD107a+CD154-IFNg+IL2+TNFa- | IFNg+ / IL2+ / TNFa- / CD107+ |
| | CD8/CD107a-CD154+IFNg+IL2+TNFa-<br>CD8/CD107a-CD154-IFNg+IL2+TNFa- | IFNg+ / IL2+ / TNFa- / CD107- |
| | CD8/CD107a+CD154+IFNg+IL2-TNFa+<br>CD8/CD107a+CD154-IFNg+IL2-TNFa+ | IFNg+ / IL2- / TNFa+ / CD107+ |
| | CD8/CD107a-CD154+IFNg+IL2-TNFa+<br>CD8/CD107a-CD154-IFNg+IL2-TNFa+ | IFNg+ / IL2- / TNFa+ / CD107- |
| | CD8/CD107a+CD154+IFNg+IL2-TNFa-<br>CD8/CD107a+CD154-IFNg+IL2-TNFa- | IFNg+ / IL2- / TNFa- / CD107+ |
| | CD8/CD107a-CD154+IFNg+IL2-TNFa-<br>CD8/CD107a-CD154-IFNg+IL2-TNFa- | IFNg+ / IL2- / TNFa- / CD107- |
| | CD8/CD107a+CD154+IFNg-IL2+TNFa+<br>CD8/CD107a+CD154-IFNg-IL2+TNFa+ | IFNg- / IL2+ / TNFa+ / CD107+ |
| | CD8/CD107a-CD154+IFNg-IL2+TNFa+<br>CD8/CD107a-CD154-IFNg-IL2+TNFa+ | IFNg- / IL2+ / TNFa+ / CD107- |
| | CD8/CD107a+CD154+IFNg-IL2+TNFa-<br>CD8/CD107a+CD154-IFNg-IL2+TNFa- | IFNg- / IL2+ / TNFa- / CD107+ |
| | CD8/CD107a-CD154+IFNg-IL2+TNFa-<br>CD8/CD107a-CD154-IFNg-IL2+TNFa- | IFNg- / IL2+ / TNFa- / CD107- |
| | CD8/CD107a+CD154+IFNg-IL2-TNFa+<br>CD8/CD107a+CD154-IFNg-IL2-TNFa+ | IFNg- / IL2- / TNFa+ / CD107+ |

| T Cell | Cytokines (%) | Cytokine combination naming |
|---|---|---|
| | CD8/CD107a-CD154+IFNg-IL2-TNFa+<br>CD8/CD107a-CD154-IFNg-IL2-TNFa+ | IFNg- / IL2- / TNFa+ / CD107- |
| | CD8/CD107a+CD154+IFNg-IL2-TNFa-<br>CD8/CD107a+CD154-IFNg-IL2-TNFa- | IFNg- / IL2- / TNFa- / CD107+ |

Overall cytokine percentage expression (%) for each T cell (CD4+, CD8+) by stimulation antigen will then be calculated as:

- For CD4+: the sum of every CD4+ cytokine combination (%) where at least one of the 4 cytokines of interest (i.e., CD154, IFNg, TNFa, and IL-2) is positive [+] (regardless of CD107a positivity). That is, every CD4+ parameter combination except for the two below where expression is negative for all 4 cytokines of interest for CD4+:
    - CD4/CD107a+CD154-IFNg-TNFa-IL-2-
    - CD4/CD107a-CD154-IFNg-TNFa-IL-2-
- For CD8+: the sum of every CD8+ cytokine combination (%) where at least one of the 4 cytokines of interest (i.e., CD107, IFNg, TNFa, and IL-2) is positive (regardless of CD154 positivity). That is, every CD8+ parameter combination except for the two below where expression is negative for the 4 cytokines of interest for CD8+:
    - CD8/CD107a-CD154+IFNg-TNFa-IL-2-
    - CD8/CD107a-CD154-IFNg-TNFa-IL-2-

Missing values will not be imputed for this analysis.

### 2.6.2. IFN-λ ELISpot

Peripheral blood mononuclear cells will also be used in IFN-γ ELISpot assays to determine the breadth of prostate cancer-specific T-cell responses (defined by number of peptide pools or individual peptides recognised). These data may be used to build immunologic models of the immune system. The total (sum over antigens) response for a participant at a given time point is calculated using the average results of the sample performed in triplicate (SFU/$10^6$ PBMC) for each stimulation antigen (i.e., PSA, PAP, 5T4, STEAP1) and is directly provided by Barinthus Bio's Immunology laboratory. As with the ICS data, results for each stimulation antigen are background-subtracted by subtracting the DMSO average result from the stimulation antigen's average result and is also directly provided by Barinthus Bio's Immunology laboratory.

A participant will be considered to have a response if the background-subtracted average result is greater than the associated positivity threshold for each sample supplied by the Barinthus Bio immunology laboratory. Missing values will not be imputed for this analysis.

### 2.6.3. Other exploratory endpoints

Exploratory endpoints, including assessments of molecular markers (eg MSI-H, BRCA and expression level of VTP-850 antigens), ctDNA and PSMA scans, will not be analysed in this phase 1 part of the study.

## 2.7. Safety Variable(s)

The planned timepoints for all safety assessments are provided in Section 1.3 of the protocol. Vital signs will include temperature, systolic and diastolic blood pressure and pulse. Blood pressure and pulse will be measured in a sitting position after 3 minutes of rest. Vital signs will be measured at Screening, Days 1, 15, 29, 43, 57, 71, 91 and Months 6 and 24. Assessments at Days 57, 71, 91 and Month 6 may be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression or in participants whose 2$^{nd}$ dose of MVA was delayed due to study pause.

A complete physical examination is performed at Screening only, and a symptom-directed physical examination will be performed at Days 1, 15, 29, 43, 57, 71 and 91 and Months 6 and 24/End of Trial visit. Assessments at days 57 and 71 may be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression or in participants whose 2$^{nd}$ dose of MVA was delayed due to study pause.

Scheduled clinical laboratory assessments will be performed using a central laboratory at Screening, Days 1, 15, 29, 36, 43, 57, 64, 71, 91 and Month 6. Assessments at days 57, 64 and 71 may be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression or in participants whose 2$^{nd}$ dose of MVA was delayed due to study pause.

Electrocardiograms (ECGs) will be performed at Screening, Days 1, 15, 29, 43, 57, 71, 91 and Month 6. Assessments at days 57 and 71 may be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression or in participants whose 2$^{nd}$ dose of MVA was delayed due to study pause.

Adverse events will be reported by participants (or, when appropriate, by a caregiver, surrogate or the participant's legally authorized representative). All AEs will be collected from the start of the first VTP-850 administration, continuing until the Month 6 visit. For participants who receive an optional third MVA dose or whose second MVA dose was delayed following the study pause, AEs will again be collected from the MVA dose until roughly four months hence (i.e., the "Additional Month 6" visit in the EDC). All SAEs will be collected from the start of the first VTP-850 administration until the last trial visit. Medical occurrences that begin before the start of the trial intervention but after obtaining informed consent will be considered part of the participant's medical history/current medical conditions. However, any medical occurrence that begins before the start of trial intervention but after obtaining informed consent that meets the criteria for seriousness and is causally related to a screening procedure will be reported with the SAE form (and will therefore have to be included on an AE form).

# 3. Estimand(s)

The ICH[1] E9 (R1) addendum on estimands[2] and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary objectives. Each estimand is defined according to the following five attributes:

1) The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
2) The **population** of participants targeted by the clinical question.
3) The **variable** (or endpoint) to be obtained for each participant that is required to address the clinical question.
4) The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
5) A **population-level summary** for the variable providing a basis for comparison between treatment conditions.

## 3.1. Estimands for the primary objective

The main estimand is defined through the following five attributes:

### 3.1.1. Treatment

The primary treatment is VTP-850 administered in three doses/regimens as follows:

**Table 2: Phase 1 Trial Cohorts**

| Cohort | | Number of Participants | Trial Intervention | |
|---|---|---|---|---|
| | | | ChAdOx1-PCAQ Day 1 | MVA-PCAQ Days 29 and 57 |
| 1 | IM/IM Low Dose | 3-6 | $5\times10^9$ vp IM | $5\times10^7$ pfu IM |
| 2 | IM/IM Full Dose | 6 | $2.5\times10^{10}$ vp IM | $2\times10^8$ pfu IM |
| 3 | IM/IV Full Dose | 6 | $2.5\times10^{10}$ vp IM | $2\times10^7$ pfu IV |

IM=Intramuscular, IV=Intravenous, pfu=plaque forming units, vp=viral particles.

### 3.1.2. Population of Participants Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 5.

### 3.1.3. Variable Obtained from Each Participant Required to Address the Clinical Question

For each participant in the study, the variable to address the clinical question is the occurrence, grade, relationship to treatment and seriousness of adverse events from the start of the first VTP-850 administration continuing until the Month 6 visit.

### 3.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following table describes how intercurrent events will be collected and handled within the analysis.

**Table 3: Handling of Intercurrent Events for the Primary Estimand**

| Intercurrent event | Data collection and analysis |
|---|---|
| Start of new therapy, such as ADT | Participants will be followed and data collected prior to the occurrence of the intercurrent event in line with a while on treatment strategy. |

### 3.1.5. Sensitivity Estimators for the Primary Estimand

Not Applicable.

### 3.1.6. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the number and proportion of participants in each treatment group with adverse events, treatment-related adverse events, ≥Grade 3 AEs, ≥Grade 3 treatment-related AEs, serious adverse events and treatment-related serious adverse events. No formal hypothesis testing will be conducted.

# 4. Analysis Populations

In accordance with ICH E3 and E9[3], the following analysis sets will be used for the analyses. The assignment of participants to the analysis sets (and whether any participant or specific data from a participant is excluded) will be determined at the pre-database-lock Data Review meeting.

## 4.1. All Screened Set

The All Screened Set will include every participant who has signed the informed consent form. The All Screened Set will be used for summaries of disposition and the associated listing.

## 4.2. Full Analysis Set

The Full Analysis Set (FAS) is based on the intent-to-treat principle and will consist of all participants who are enrolled into the trial and who received at least one dose of VTP-850. FAS participants are analysed according to the dose regimen that the participant was allocated.

The FAS will be used for summaries and analyses of efficacy endpoints that are not related to PSA.

## 4.3. Safety Analysis Set

The Safety Analysis Set (SAF) will consist of all participants who received at least one dose of VTP-850. SAF participants are analyzed according to the dose regimen the participant received.

The SAF will be used for summaries and analysis of demographics and baseline characteristics, treatments and medications, and primary safety endpoints including analyses of adverse events, laboratory safety tests and vital signs.

## 4.4. Efficacy Evaluable Set

The Efficacy Evaluable Set (EES) will consist of all participants in the FAS who had one baseline measurement of PSA and at least one post-baseline measurement of PSA. EES participants are analysed according to the dose regimen the participant was allocated.

The EES will be used for analyses of secondary efficacy endpoints which examine PSA response.

### 4.5. Per Protocol Set

Due to the small number of participants in the phase I part of this study, the Per Protocol Set (PPS), defined as participants in the FAS who received all planned doses of VTP-850 (Days 1, 29 and 57) at the protocol-defined dose and within the protocol-defined window (participants with delayed dosing due to study pause during the phase 1 portion of the trial as per protocol Section 6.12 will be considered to have dosing within the protocol-defined windows) and do not have any important protocol deviations leading to exclusion from the PPS. PPS participants are analyzed according to the dose regimen the participant received.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important and non-important protocol deviations are referred to as major and minor protocol deviations, respectively, in the protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the correctness, accuracy, and / or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being as outlined in the protocol deviation management plan and associated protocol deviation guidelines document. A full list of the important protocol deviations, and the subset that will lead to removal from the PPS, is described in the protocol deviation management plan. Important protocol deviations will be confirmed at review meetings before locking the clinical database.

### 4.6. Immunogenicity Analysis Set

The immunogenicity analysis set will consist of all participants who have available immunogenicity data at baseline and at least one post-baseline measurement and do not have any important protocol deviations that might impact the results of the immunological analysis as determined during population review meetings before database lock.

# 5. Data Handling

## 5.1. Time Points and Visit Windows

### 5.1.1. General Definitions

During the intervention period, assessment days are calculated relative to the date of the previous VTP-850 dose. During the screening, short-term and long-term follow-up periods, all assessment days will be relative to the first dose of treatment including assessments prior to the first dose of treatment.

During the screening, intervention, short-term and long-term follow-up periods, Day 1 is defined as the first dose of treatment except for the calculation of study windows described in Section 5.1.4 where, during the intervention period, day 1 will be defined relative to the first, second, third and optional fourth dose of VTP-850. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. There is no Day 0.

The date of the first dose of treatment for each participant will be taken from the ChAdOx1-PCAQ Administration eCRF page. The date of the last dose of treatment for each participant will be the latest date from the ChAdOx1-PCAQ administration or MVA-PCAQ administration eCRF pages.

### 5.1.2. Screening Period

For all participants, the screening period is defined as the period from informed consent to the first administration of treatment. For some variables, such as data from scans, data are allowed prior to the date of informed consent provided the procedures met the protocol-specified criteria. For some variables, data from more than one assessment within the screening period can be collected prior to the first administration of treatment. The baseline value for a variable is defined as the last non-missing value collected before the first administration of treatment.

Assessments carried out on day of first administration of treatment are considered to have taken place before the first administration of treatment, except for vital signs recorded as post-dose and treatment-emergent AEs.

### 5.1.3. Intervention Period

Data collected at Day 1 will be assigned to the Intervention Period if post-dose is recorded on the eCRF page. Adverse events starting on Day 1 (unless specified as starting before the dosing time), post-dose vital signs, and medications starting on Day 1 will be assigned to the Intervention Period.

The Intervention Period is defined as the period from the date / time of the first administration of treatment up to the Day 91 clinic visit. The short-term follow-up period is defined from after the Day 91 visit up to and including the earliest of 6 months after the first administration of treatment, development of unequivocal metastatic prostate cancer or until the start of new therapy, such as ADT. The long-term follow-up period will be defined for participants who have a PSA response in the first 6 months for an additional 18 months up to 24 months after the first administration of treatment, or until the start of new therapy such as ADT or development of unequivocal metastatic prostate cancer.

### 5.1.4. Visit Windows

Tables 5 to 7 provides the relative study day ranges to be applied to the assessment / sample collection date to derive the analysis timepoint for by timepoint analyses of PSA / laboratory / vital signs and symptom-directed physical examination.

The following considerations are to be followed when deriving the analysis timepoints:

- The relative day number of the assessment lies between the lower and upper boundary of the visit window (the boundary values are included)
- Both scheduled and unscheduled assessments are included for visit windowing
- If there are two or more valid assessments for a defined window the following rules will be applied:
    - Assessments with missing data and assessments marked “Not Done” will be considered as providing a missing response and are not permitted to be assigned to a visit window.
    - The worst value (e.g. out of reference range preferred to within range; abnormal preferred to normal) will be used in each window. If multiple assessments fall within the same window with equal value, then the first non-missing value will be used for the summary.

- Participants who have an optional third dose of MVA-PCAQ due to an initial PSA response followed by progression will have an additional day 57, 64 and 71 visit. If two assessments are in both the additional day 64 and day 91 visit window or day 71 and day 91 visit window then the first assessment will be assigned to day 64 or 71 and the second to day 91. If only one assessment is available in both windows then this will be assigned to day 91.
- Participants who have had a study pause will not have visit windowing applied for visits after this window and will have analysis visit assigned based on the recorded visit name in the eCRF.

**Table 4: Definition of Visit Windows for PSA Assessments**

| Period | Visit | Target Day of Visit | Protocol Visit Windows | Analysis Visit Window |
|---|---|---|---|---|
| Screening | Screening | Day –1[a] | Day -43 to -1 | Not Applicable |
| Intervention | Baseline | Day 1[a] | Day 1[a] | Prior to or on Day 1[a] |
| Intervention | Day 29 | Day 1[b] | Day 1[b] | Day 1[b] |
| Intervention | Day 57 | Day 1[c] | Day 1[c] | Day 1[c] |
| Intervention | Day 64 | Day 8[c] | Day 5 to 9[c] | Day 2 to 14[c] |
| Intervention | Additional Day 57 | Day 1[d] | Day 1[d] | Day 1[d] |
| Intervention | Additional Day 64 | Day 8[d] | Day 5 to 9[d] | Day 2 to 14[d] |
| Intervention | Day 91 | Day 91[a] | Day 89 to 91[a] | Day 78 to 104[a] |
| Short-Term Follow-Up | Month 4 | Day 120[a] | Day 113 to 127[a] | Day 105 to 135[a] |
| Short-Term Follow-Up | Month 5 | Day 150[a] | Day 143 to 157[a] | Day 136 to 165[a] |
| Short-Term Follow-Up | Month 6 | Day 180[a] | Day 173 to 187[a] | Day 166 to 195[a] |
| Long-Term Follow-Up | Month 7 | Day 210[a] | Day 203 to 217[a] | Day 196 to 225[a] |
| Long-Term Follow-Up | Month 8 | Day 240[a] | Day 233 to 247[a] | Day 226 to 255[a] |
| Long-Term Follow-Up | Month 9 | Day 270[a] | Day 263 to 287[a] | Day 256 to 285[a] |
| Long-Term Follow-Up | Month 10 | Day 300[a] | Day 293 to 307[a] | Day 286 to 315[a] |
| Long-Term Follow-Up | Month 11 | Day 330[a] | Day 323 to 337[a] | Day 316 to 345[a] |
| Long-Term Follow-Up | Month 12 | Day 360[a] | Day 353 to 367[a] | Day 346 to 400[a] |
| Long-Term Follow-Up | Month 14 | Day 420[a] | Day 413 to 427[a] | Day 401 to 440[a] |
| Long-Term Follow-Up | Month 16 | Day 480[a] | Day 473 to 487[a] | Day 441 to 509[a] |
| Long-Term Follow-Up | Month 18 | Day 540[a] | Day 533 to 547[a] | Day 510 to 569[a] |
| Long-Term Follow-Up | Month 20 | Day 600[a] | Day 593 to 607[a] | Day 570 to 629[a] |
| Long-Term Follow-Up | Month 22 | Day 660[a] | Day 653 to 667[a] | Day 630 to 689[a] |
| Long-Term Follow-Up | Month 24 | Day 720[a] | Day 713 to 727[a] | Day 690 to 749[a] |

[a] Relative to first dose of treatment
[b] Relative to second dose of treatment
[c] Relative to third dose of treatment
[d] Relative to optional fourth dose of treatment

**Table 5: Definition of Visit Windows for Laboratory Assessments**

| Period | Visit | Target Day of Visit | Protocol Visit Windows | Analysis Visit Window |
|---|---|---|---|---|
| Screening | Screening | Day –1[a] | Day -43 to -1[a] | Not Applicable |
| Intervention | Baseline | Day 1[a] | Day 1[a] | Prior to or on Day 1[a] |
| Intervention | Day 15 | Day 15[a] | Day 12 to 16[a] | Day 11 to 27[a] |
| Intervention | Day 29 | Day 1[b] | Day 1[b] | Day 1[b] |
| Intervention | Day 36 | Day 8[b] | Day 6 to 10[b] | Day 2 to 11[b] |
| Intervention | Day 43 | Day 15[b] | Day 12 to 16[b] | Day 11 to 27[b] |
| Intervention | Day 57 | Day 1[c] | Day 1[c] | Day 1[c] |
| Intervention | Day 64 | Day 8[c] | Day 6 to 10[c] | Day 2 to 11[c] |
| Intervention | Day 71 | Day 15[c] | Day 12 to 16[c] | Day 11 to 27[c] |
| Intervention | Additional Day 57 | Day 1[d] | Day 1[c] | Day 1[c] |
| Intervention | Additional Day 64 | Day 8[d] | Day 6 to 10[c] | Day 2 to 11[c] |
| Intervention | Additional Day 71 | Day 15[d] | Day 12 to 16[c] | Day 11 to 27[c] |
| Intervention | Day 91 | Day 91[a] | Day 89 to 91[a] | Day 78 to 104[a] |
| Short-Term Follow-Up | Month 6 | Day 180[a] | Day 173 to 187[a] | Day 166 to 195[a] |

[a] Relative to first dose of treatment
[b] Relative to second dose of treatment
[c] Relative to third dose of treatment
[d] Relative to optional fourth dose of treatment

**Table 6: Definition of Visit Windows for Vital Sign Assessments/Symptom-directed Physical Examination**

| Period | Visit | Target Day of Visit | Protocol Visit Windows | Analysis Visit Window |
|---|---|---|---|---|
| Screening | Screening | Day –1[a] | Day -43 to -1[a] | Not Applicable |
| Intervention | Baseline | Day 1[a] | Day 1[a] | Prior to or on Day 1[a] |
| Intervention | Day 15 | Day 15[a] | Day 12 to 16[a] | Day 11 to 27[a] |
| Intervention | Day 29 | Day 1[b] | Day 1[b] | Day 1[b] |
| Intervention | Day 43 | Day 15[b] | Day 12 to 16[b] | Day 11 to 27[b] |
| Intervention | Day 57 | Day 1[c] | Day 1[c] | Day 1[c] |
| Intervention | Day 71 | Day 15[c] | Day 12 to 16[c] | Day 11 to 27[c] |
| Intervention | Additional Day 57 | Day 1[d] | Day 1[c] | Day 1[c] |
| Intervention | Additional Day 71 | Day 15[d] | Day 12 to 16[c] | Day 11 to 27[c] |
| Intervention | Day 91 | Day 91[a] | Day 89 to 91[a] | Day 78 to 104 [a] |
| Short-Term Follow-Up | Month 6 | Day 183[a] | Day 176 to 190[a] | Day 121 to 457[a] |
| Long-Term Follow-Up | Month 24 | Day 731[a] | Day 724 to 738[a] | Day 458 to 738[a] |

[a] Relative to first dose of treatment
[b] Relative to second dose of treatment
[c] Relative to third dose of treatment
[d] Relative to optional fourth dose of treatment

## 5.2. Handling of Dropouts, Missing Data, and Outliers

### 5.2.1. Handling of Missing Efficacy Data

Participants with missing PSA data at the Month 8 visit will have a durable PSA response imputed if they have a confirmed PSA response at the latest non-missing PSA collection preceding the Month 8 visit and the first non-missing PSA collection following the Month 8 visit. Otherwise, if participants are missing PSA data at Month 8, they will be treated as non-responders for the main analysis. A confirmed PSA response is defined as a ≥50% reduction in serum PSA compared to baseline and measured twice consecutively, at least 2 weeks apart. Details regarding the analyses of PSA are provided in Section 6.6.

### 5.2.2. Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are given in Section 6.7.2. Unknown or partial medication and AE date imputations are given below and to be used only

for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

### 5.2.3. Handling of Partial and Missing Dates for Adverse Events, Prior / Concomitant Medications, Missing Adenocarcinoma History Dates

Missing or Partial Adverse Event and Prior / Concomitant Medication Start Dates

Missing and / or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this will be done as follows:

For a missing / incomplete start date the earliest date of the following will be imputed:

- The later date of the earliest possible start date and the date of first dose of treatment.
- The latest possible start date (defined below).
- The latest possible stop date (defined below).

For a missing / incomplete stop date the latest date of the following will be imputed:

- The earlier date of the latest possible stop date and the date of last dose of treatment.
- The earliest possible stop date (defined below).
- The earliest possible start date (defined below).

Here, the earliest possible date is defined as:

- The date itself if available.
- The date of the first day of the month, if month and year are available but the day is missing.
- The date of the first day of the year, if year is available but day and month are missing.
- Day of informed consent, if the date is completely missing.

The latest possible date is defined as:

- The date itself if available.
- The date of the last day of the month, if month and year are available but the day is missing.
- The date of the last day of the year, if year is available but day and month are missing.
- Date of last known date on the study for the participant plus one year, if the date is completely missing.

Missing Adenocarcinoma History Dates

Missing adenocarcinoma history dates for the date of initial diagnosis of prostate adenocarcinoma, historic tumour sample collection date, radical prostatectomy date and date of nonmetastatic (M0) disease confirmed will be imputed as follows:

- The date itself if available.
- The date of the 15th of the month, if month and year are available but the day is missing.
- The date of 01-July of the year, if year is available but day and month are missing.
- No imputation, if the date is completely missing.

# 6. Statistical Methods

## 6.1. General Principles

All data processing, summarization and analyses will be performed using Fortrea's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, 25$^{th}$ percentile, 75$^{th}$ percentile, minimum (min) and maximum (max), for those participants with data. The 25$^{th}$ and 75$^{th}$ percentiles will only be presented when the denominator is at least 10 participants.

For qualitative variables, the number (n) and percentage (%) of participants with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. The number of participants in the analysis population will be used as the denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

All statistical comparisons will be made using two-sided tests at the $\alpha$=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided.

All laboratory test results will be received from central laboratories, and the results will be provided in both standard internal and conventional units. For the TFLs, the results will be summarized or presented in International System of Units (SI) units. Refer to Appendix of the TFLs mock shells for the SI unit corresponding to each laboratory test.

Refer to Appendix of the TLF shells for the precision level in which each laboratory test is reported by the central laboratories.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study. Please refer to "2. General Format Guidelines" section within TFL shells for more details on presentation of results.

In summary tables, participants will be presented by the following treatment groups::

- IM/IM Low Dose
- IM/IM Full Dose
- IM/IV Full Dose

If a participant does not receive a second dose of investigational product they will be assigned to the treatment group IM/IM Full.

In listings, participants will be presented by the following treatment groups:

- Cohort 1: IM/IM Low Dose
- Cohort 2: IM/IM Full Dose
- Cohort 3: IM/IV Full Dose

### 6.2. Participant Disposition and Data Sets Analyzed

Participant disposition will be summarized by treatment group and overall, where appropriate, for the All Screened Set. The following information will be reported:

- Number of participants for the following categories:
  - Screened,
  - Screen Failure ('Screen Failure' CRF page lists "Eligibility Evaluation was not completed");
- Number and percentage of participants for the following categories:
  - Assigned to treatment (participants who have not screen failed and have a cohort assigned),
  - Treated (Received one or more doses of VTP-850),
  - Not treated,
  - Completed Short-Term Follow-Up,
  - Discontinued Short-Term Follow-Up,
  - Reason for discontinuing Short-Term Follow-Up;
- Number and percentage of participants included in, and excluded from, each study population together with the reasons for exclusion from the analysis set;
- Number and percentage of participants who completed / did not complete the intervention period, including the reasons for treatment discontinuation (as collected on the End of Treatment CRF page under question "If the participant did not complete the intervention period as per protocol, provide the main reason for discontinuation"), and a summary of number of doses received (ChAdOx1-PCAQ and MVA-PCAQ summarised separately);
- Number and percentage of participants who met / did not meet all eligibility criteria, together with the criteria not met;
- Number and percentage of participants at each site.

A participant will be regarded as having completed Short-Term Follow-Up provided a follow-up visit eCRF page with a nominal visit of either "Month 6" or "End of Treatment" is recorded where a participant status does not equal "Lost to follow-up". For the final analysis, participants missing reason for study completion/discontinuation on an End of Study eCRF form from the question "Reason for study completion/discontinuation" will be considered to have completed the study. For dry run and interim analyses, participants missing reason for

study completion/discontinuation on an 'Disposition – End of Study' eCRF page will be considered to be ongoing in the study.

A listing of all participants with their treatment and study completion status, including the respective reasons for treatment and study discontinuation, will be presented for the FAS.

A listing of all screen-failed participants with their reasons for screen failure will be presented for the All Screened Set. A separate listing of participants who failed at least one inclusion / exclusion criterion including a text description of the criterion failed will be presented for the All Screened Set.

A listing of all participants, their inclusion in each analysis set and reasons for exclusion from analysis sets, if excluded from an analysis set, will be presented for the All Screened Set.

### 6.3. Protocol Deviations

All important protocol deviations will be summarized for the SAF by study cohort and overall as described below:

- The number of unique participants with at least one important protocol deviation as well as the number of participants in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

Important protocol deviations which lead to exclusion from the PPS will be summarized for the SAF by study cohort and overall as described below:

- The number of unique participants with at least one important protocol deviation leading to exclusion from the per protocol set as well as the number of participants in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all participants with one or more important / non important protocol deviations will be presented for the Safety Analysis Set. Protocol deviations which resulted in removal from the PPS will be indicated.

### 6.4. Demographic and Other Baseline Characteristics

#### 6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the Safety Analysis Set by treatment group and overall as described below. All missing data will be presented as part of a missing category. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years) at time of informed consent
- Height (cm) at screening visit
- Weight (kg) at screening visit

- Body mass index (kg/m$^2$) at screening visit, calculated as (body weight / height$^2$) where weight is in kg and height is in m and presented to one decimal precision.

Total counts and percentages of participants will be presented for the categorical variables of:

- Age group (years):
  - < 65
  - ≥ 65 to < 75
  - ≥75
- Race
- Ethnicity

Demographic characteristics will be listed for the Safety Analysis Set.

### 6.4.2. Baseline Characteristics

Baseline characteristics will be summarized for the Safety Analysis Set by treatment group and overall as described below. All missing data will be presented as part of a missing category. Missing categories will only be displayed if missing data are present.

Standard descriptive statistics will be presented for the continuous variables of:

- Time from date of initial diagnosis of prostate adenocarcinoma to informed consent (months) [Calculated as (date of informed consent – date of initial diagnosis of prostate adenocarcinoma + 1)/30.4375]
- If historic tumour sample has been collected: Time from historic tumour sample collection date to informed consent (months) [Calculated as (date of informed consent – date of historic tumour sample collection + 1)/30.4375]
- If radical prostatectomy has been performed: Time from date of radical prostatectomy to informed consent (months) [Calculated as (date of informed consent – date of radical prostatectomy + 1)/30.4375]
- If non-metastatic (M0) disease has been verified: Time from non-metastatic disease confirmed to informed consent (months) [Calculated as (date of informed consent – date of non-metastatic disease confirmed [Date Nonmetastatic (M0) Disease Confirmed on Prostate Adenocarcinoma History eCRF page]+ 1)/30.4375]
- eCRF PSA Doubling Time (months)
- Independently calculated PSA doubling time (months): PSA doubling time will be independently calculated based on historic PSA values collected on the Prostate Adenocarcinoma History eCRF page. The 3 most recent PSA values will be used to calculate doubling time where the date of assessment ≥ (date of informed consent – 2*365.25). The first included date of assessment, *date1*, will be treated as Time 0

and other assessments will have time, *t*, calculated as *datej-date1+1*. The linear regression model will be fitted as:

$\ln(PSA(t))=\ln(PSA(0))+\beta t$.

The PSA doubling time (months) will be calculated as: $\ln 2/(\beta \times 30.4375)$.

Total counts and percentages of participants will be presented for the categorical variables of:

- Confirmation of adenocarcinoma (Histologically, Cytologically)
- Radical prostatectomy (Yes, No)
- Nonmetastatic (M0) disease verified (Yes, No)
- Previous treatment with radiation (Yes, No)
    - Type of radiotherapy (Definitive external beam radiation, Salvage external radiation therapy)
- Previous treatment with brachytherapy (Yes, No)
    - Low Dose, High Dose
- Radical Prostatectomy (Yes) (External Beam Radiotherapy, No External Beam Radiotherapy) [From the prostate adenocarcinoma history eCRF page where "Was the participant treated by radiation? Is Yes/No]
- Radical Prostatectomy (No) (Brachytherapy Only, External Beam Radiotherapy Only, Brachytherapy and External Beam Radiotherapy)
- Any other prior malignancy within the last 5 years (Yes, No)
- T Stage (T1, T2, T3, T4)
- Gleason Score ≤6, 7, 8, 9, 10)
- Gleason pattern (≤6, 3+4, 4+3, 8, ≥9)
- Baseline PSA (ng/ml) (<0.5, 0.5-1, 1-2, 2-5, 5-10, 10-20, >20) [Using the serum PSA assessment from the screening period]
- PSA doubling time as recorded in the 'Prostate Adenocarcinoma History' eCRF page (0-<6 months , 6-12 months, >12 months)

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

The Gleason pattern categories will combine categories captured in the 'Protate Adenocarcinoma History' eCRF page gleason pattern question as:

- ≤6 (Captured as 'Less than or Equal to 3+3')
- 3+4
- 4+3
- 8 (Captured as '4+4', '3+5', '5+3')
- ≥9 (Captured as '4+5', '5+4', '5+5')

Baseline characteristics will be listed for the Safety Analysis Set.

### 6.4.3. Medical History

Medical history is defined as any condition that the participant may have had prior to start of first dose of VTP-850 in the study, including any chronic conditions diagnosed prior to entry in the study.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 25.1 or later version]. Medical history records will be summarized for the Safety Analysis Set by treatment group and overall as follows:

- The number and percentage of participants with at least one medical history record will be presented.
- The number and percentage of participants with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-participant and within-participant by medical history start date for the Safety Analysis Set.

### 6.4.4. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary, Format B3 [Version September 2022 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes. As per protocol Section 6.10, this will include all vaccines that the participants received any time from 6 months prior to enrolment and any time during the trial. Any prior adenoviral-vectored vaccine administered at any time should be recorded (e.g. COVID-19 vaccines made by Janssen/Johnson & Johnson or by AstraZeneca).

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken up to 30 days prior to day 1 with a stop date prior to the start of the Intervention Period.
- Concomitant medications are those with a start date on or after the start of the Intervention Period, or those with a start date before the start of the Intervention Period and either a stop date on or after the start of the Intervention Period, or are ongoing at the end of the study.

Prior procedures and concomitant procedures are defined as follows:

- Prior procedures are those taken up to 30 days prior to day 1 with a stop date prior to the start of the Intervention Period.
- Concomitant procedures are those with a start date on or after the start of the Intervention Period, or those with a start date before the start of the Intervention Period and either a stop date on or after the start of the Intervention Period, or are ongoing at the end of the study.

See Section 5.2.3 for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized separately for the Safety Analysis Set by treatment group and overall as follows:

- The number and percentage of participants with at least one prior / concomitant medication will be presented.
- The number and percentage of participants with at least one prior / concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications, prior procedures and concomitant medications will be listed separately for the Safety Analysis Set. In the listings the relative start and stop day of prior / concomitant medication use will be calculated relative to the first dose date and time of VTP-850. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Adenoviral-vectored vaccines will be marked in the listings and identified via clinical review of the prior and concomitant medications prior to database lock. Prior and concomitant procedures will be listed only.

### 6.5. Measurements of VTP-850 Compliance

VTP-850 is administered at the site, under the supervision of qualified personnel, and so treatment compliance measurement is not applicable.

### 6.6. Efficacy

No adjustment for multiplicity will be made. Without adjustment for multiplicity, results should be interpreted with caution as the probability of a type I error increases.

#### 6.6.1. Primary Efficacy Analysis

Primary Efficacy Analysis is not applicable.

### 6.6.2. Secondary Efficacy Analysis

#### 6.6.2.1. PSA Response to VTP-850

The number, proportion and 90% confidence intervals (CI) of participants with a confirmed PSA response, defined as a ≥50% reduction in serum PSA compared to baseline and measured twice consecutively, at least 2 weeks apart, will be summarized by timepoint (using visit windows defined in Section 5.1) and overall for each treatment group using the EES. The proportion at each time point will present the participants who have the 1st (if confirmed at least 2 weeks later) measurement where the ≥50% reduction in serum PSA has been met compared to baseline. Percentage change in PSA will be calculated as 100×(PSA value (ng/ml) at visit i - PSA value at baseline)/(PSA value at baseline). The 90% CIs will be calculated using Jeffrey's confidence limits. The maximum percentage change in PSA from baseline will be summarized continuously by treatment group. A waterfall plot of maximum percentage change in PSA from baseline will be produced by treatment group with bars of the waterfall plot produced using different colours to represent prior radical prostatectomy or definitive external beam radiation (Yes, No). Per cohort, a spaghetti plot will display each participant's percentage change in PSA (e.g. each patient's baseline measurement will display as 100%) by the number of days since the day 1 dosing visit. On each participant's line, a marker will indicate the study day each dose occurred.

Example of this calculation of confirmed PSA response are displayed in Table 7 and Table 8.

**Table 7: Calculation of PSA Response Example**

| Participant | Timepoint | Study Day | PSA Value (ng/mL) | PSA change from baseline | PSA absolute change from nadir | PSA percent change from nadir |
|---|---|---|---|---|---|---|
| 1 | Baseline | 1 | 1.5 | | | |
| 1 | Day 29 | 29 | 1.6 | 6.67% | | |
| 1 | Day 57 | 57 | 1.0 | -33.33% | | |
| 1 | Day 64 | 64 | 0.9 | -40.00% | | |
| 1 | Month 4 | 122 | 0.8 | -46.67% | | |
| 1 | Month 5 | 153 | 0.2 | -86.67% | | |
| 1 | Month 6 | 164 | 0.2 | -86.67% | | |
| 1 | Month 7 | 215 | 0.3 | -80.00% | 0.1 | 50.00% |
| 1 | Month 8 | 246 | 0.3 | -80.00% | 0.1 | 50.00% |
| 1 | Month 9 | 271 | 0.5 | -66.67% | 0.3 | 150.00% |

- Responder = Yes
- First observed PSA response = Month 5

- PSA progression (Defined in Section **Error! Reference source not found.**) = Month 9 (since there's a ≥25% increase from PSA nadir AND an absolute increase of ≥0.2 ng/mL)
- Durable PSA response at Month 8 (Defined in Section 6.6.2.2) = Yes (since a confirmed PSA response has occurred and the criteria for PSA progression has not been met

**Table 8: Calculation of PSA Response Example**

| Participant | Timepoint | Study Day | PSA Value (ng/mL) | PSA change from baseline | PSA absolute change from nadir | PSA percent change from nadir |
|---|---|---|---|---|---|---|
| 1 | Baseline | 1 | 1.6 | | | |
| 1 | Day 29 | 29 | 1.3 | -18.75% | | |
| 1 | Day 57 | 57 | 1.05 | -34.38% | | |
| 1 | Day 64 | 64 | 0.90 | -43.75% | | |
| 1 | Month 4 | 122 | 0.80 | -50.00% | | |
| 1 | Month 5 | 152 | 0.80 | -50.00% | | |
| 1 | Month 6 | 164 | 0.81 | -49.38% | 0.01 | 1.25% |
| 1 | Month 7 | 226 | 0.82 | -48.75% | 0.02 | 2.50% |
| 1 | Month 8 | 256 | 0.85 | -46.88% | 0.05 | 6.25% |
| 1 | Month 9 | 282 | 0.75 | -53.13% | -0.05 | -6.25% |

- Responder = Yes
- First observed PSA response = Month 4
- PSA progression = No PSA progression
- Response at Month 8 = Yes (A confirmed PSA response has occurred and no PSA progression)

#### 6.6.2.2. Durable PSA Response to VTP-850 at Month 8

If more than three participants have a confirmed PSA response at month 6 then the number, proportion and 90% CIs of participants with a durable PSA response (having a confirmed PSA response without PSA progression or on before Month 8) will be presented for each treatment group using the EES. Participants with missing PSA data at Month 8 will have a durable PSA response imputed as described previously in Section 5.2.1. Otherwise, if participants are missing PSA data at Month 8 they will be treated as non-responders. The same summary will also be presented among participants who have a durable response at Month 6.

### 6.6.3. Sensitivity Analyses for the Secondary Efficacy Analysis

Not Applicable.

### 6.6.4. Exploratory Analysis

#### 6.6.4.1. Immunogenicity Response to VTP-850

These analyses will be presented using the Immunogenicity analysis set both overall and separately by whether participants had or did not have an observed PSA response.

Background-subtracted overall percentage cytokine expression will be presented for each T cell (CD4+ and CD8+) and stimulation antigen (PSA, PAP, 5T4, STEAP1). Descriptive statistics including n, mean, standard deviation, median, minimum, maximum, and 95% CI for the median based on order statistics will be presented for absolute values, change from baseline, and fold change from baseline at all planned time points (Days 1, 29, 36, 57, 64, 91 and Months 8 and 12). Fold change for values i and j is defined as:

(Value j/Value i)-1.

Where value j is the cytokine expression value at a non-baseline timepoint and value i is the cytokine expression value at day 1. When value i is 0 a small constant, λ, will be added to the calculation. λ=0.5×min (non-zero value for all participants at all time points). In this case fold change will be calculated as:

((Value j + λ)/(Value i+ λ))-1.

DMSO (i.e. background) percentage cytokine expression will be presented similarly to background-subtracted overall cytokine response.

Graphical summaries using dot plots for the background-subtracted overall percentage cytokine expression above will be presented by planned time point separately for each T cell and stimulation antigen. The median overall cytokine response (%) per treatment group will be represented by a horizontal line. A dot plot will also be provided for DMSO (i.e., background) overall cytokine response (%) results.

In addition, the median background-subtracted overall cytokine response for the stimulation antigens (PSA, PAP, 5T4, STEAP1) will be displayed altogether in a stacked bar plot for PSA responders and for non-responders by planned time point.

The 15 background-subtracted cytokine combinations (%) (**Error! Reference source not found.**) and background-subtracted overall cytokine response (%) at Day 35 and Day 64 will be presented using polyfunctional profile plots separately for each T cell and stimulation antigen. Each of the cytokine combinations will be presented under the plot using Boolean values (+, -).

#### 6.6.4.2. ELISpot response

These analyses will be presented using the Immunogenicity analysis set both overall and separately by whether participants had or did not have an observed PSA response.

Average background-subtracted antigen-specific IFNg ELISpot response (SFU/$10^6$ PBMC) will be presented for each stimulation antigen (PSA, PAP, 5T4, STEAP1). Descriptive statistics including n, mean, standard deviation, median, minimum, maximum, and 95% CI for the median based on order statistics will be presented for absolute values, change from baseline, and fold change from baseline at all planned time points (Days 1, 29, 36, 57, 64, 91 and Months 8 and 12). Fold change for values i and j is defined as:

(Value j/Value i)-1.

Where value j is the IFNg ELIspot response value at a non-baseline timepoint and value i is the cytokine expression value at day 1. When value i is 0 a small constant, λ, will be added to the calculation. λ=0.5×min(non-zero value for all participants at all time points). In this case fold change will be calculated as:

((Value j + λ)/(Value i+ λ))-1.

To identify statistically significant differences between baseline and Days 35 and 64, a Wilcoxon signed-rank test using change from baseline will be performed for PSA responders and for non-responders for each stimulation antigen.

Like the graphical summaries described for the ICS analysis, for average background-subtracted antigen specific IFNg ELISpot response (SFU/$10^6$ PBMC) a dot plot will be presented by planned time point separately for each stimulation antigen (PSA, PAP, 5T4, STEAP1).

A stacked bar chart will also be displayed for the median total (pooled over antigens) response (SFU/$10^6$ PBMC) by planned time point for PSA responders and non-responders.

In addition, a line plot of mean ± SD of the total (pooled over antigens) response (SFU/$10^6$ PBMC) for each treatment will be displayed by planned time point.

A summary of the number and percentage of participants who meet the responder criteria (i.e., those with a background-subtracted average result greater than the positivity threshold) will be presented at all planned time points.

The average background-subtracted antigen-specific IFNg ELISpot responses (SFU/$10^6$ PBMC) will be listed by stimulation antigen for each participant at each time point.

## 6.7. Safety

All participants are to remain on study through month 6 or the start of new therapy, such as ADT, or until development of unequivocal metastatic prostate cancer. Consequently,

adverse event collection will be discontinued for participants who discontinue from follow-up after the start of new therapy.

### 6.7.1. Extent of Exposure

Duration of exposure will be defined in days as:
Exposure (days) = [date of last dose – date of first dose] + 1

Number and percentage of participant with the following treatment exposure will be calculated:

- 1 ChAdOx1-PCAQ dose only
- 1 ChAdOx1-PCAQ dose + 1 MVA-PCAQ dose
- 1 ChAdOx1-PCAQ dose + 2 MVA-PCAQ doses
- 1 ChAdOx1-PCAQ dose + 3 MVA-PCAQ doses

The number and percentage of participants where the 1st MVA dose was and was not received within the protocol-defined window (Days 27 to 31 from first dose), the 2nd MVA dose was and was not received within the protocol-defined window (Days 55 to 59) and where all planned MVA doses were received within the protocol-defined windows will be presented. Because the timing of the optional third MVA dose is variable depending on when PSA progression occurs, it will not be considered when summarizing timing of the dose relative to protocol windows. Participants whose 2nd dose of MVA was delayed due to study pause will be included in the denominator for 2nd MVA dose (but will be excluded from numerator as dose was received outside protocol-defined window).

Study treatment administration data will be listed for the Safety Analysis Set. The listing will include date/time of administration, the number of days since the previous study dose, the IMP type (ChAdOx1 vs MVA), the route of administration, the planned and total dose and whether the drug was given as per protocol and details if it was not including other specified information.

### 6.7.2. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [version 25.1 or later]:

- Treatment-emergent AEs (TEAEs) are events with start date on or after the first dose of VTP-850 and reported as not starting before first treatment.
- Treatment-Emergent Serious AEs (TESAEs) will be defined as TEAEs regarded by the investigator as Serious = “Yes”.
- The relationship between a TEAE and VTP-850 is assessed as related or not related. A treatment-related TEAE will be defined as a TEAE considered by the investigator related to treatment.

- Assessment of AE severity / intensity will be based on the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE[4], version 5.0). Severe TEAEs are defined as TEAEs assessed as being "Grade 3 / Grade 4 / Grade 5" in intensity.
- TEAEs leading to discontinuation of treatment are defined as TEAEs where "Action Taken With Study Treatment" is indicated as "Drug Withdrawn".

Adverse events will be summarized for the Safety Analysis Set by treatment group and overall as follows:

- An overview of TEAEs including the number and percentage of participants with at least one of each mentioned TEAE type:
  - Any TEAE
    - Leading to discontinuation of study treatment
    - Leading to death
    - Grade 1 severity (mild)
    - Grade 2 severity (moderate)
    - Grade 3 severity (severe)
    - Grade 4 severity (life-threatening or disabling)
    - Grade 5 severity (death related to TEAE)
  - Any study treatment-related TEAE
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any serious TEAE
    - Leading to death
  - Any serious study treatment-related TEAE
    - Leading to death

- The number and percentage of participants reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs:
  - TEAEs
  - TEAEs Leading to Discontinuation of Study Treatment
  - TEAEs Leading to Death
  - TEAEs by Maximum Severity
  - Treatment-related TEAEs
  - Treatment-related TEAEs by Maximum Severity
  - Treatment-related TEAEs Leading to Discontinuation of Study Treatment
  - Treatment-related TEAEs Leading to Death
  - Serious TEAEs
  - Serious TEAEs Leading to Discontinuation of Study Treatment
  - Serious TEAEs Leading to Death
  - Study Treatment Related Serious TEAEs
  - Study Treatment Related Serious TEAEs Leading to Death

- Study Treatment Related Serious TEAEs Leading to Discontinuation of Study Treatment
-

- The number and percentage of participants who died will be summarized by the primary reason of death.

In the above summaries, participants with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, participants with more than one TEAE within a particular PT are counted only once for that PT, respectively. Overall summaries of "Any TEAE" and "Any study treatment-related TEAE" will only include participants at the maximum severity.

For summaries by maximum severity, participants with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included in the counts of the 'Number of Participants with at least one TEAE', 'System Organ Class' and 'Preferred Term' rows of the summary but they will not be included in the counts by severity.

The following tables will also be presented by administration (i.e. ChAdOx1-PCAQ dose, 1st MVA-PCAQ dose, 2nd MVA-PCAQ dose, 3rd MVA-PCAQ dose), for TEAEs that start within 28 days of each administration (e.g. summarizing TEAEs which occurred from ChAdOx1-PCAQ dose up to the earliest of 1st MVA-PCAQ dose or 28 days following the first dose). The denominator will be the number of participants who have received that dose:

- TEAEs
- TEAEs by Maximum Severity
- Treatment-related TEAEs
- Treatment-related TEAEs by Maximum Severity
- Serious TEAEs
- Study Treatment Related Serious TEAEs

Summaries by SOCs and PTs will be sorted by SOCs alphabetically (MedDRA) and PTs within SOC by descending order of total incidence. Where preferred terms tie, PTs will be sorted alphabetically.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed using the Safety Analysis Set. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated.

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of Serious TEAEs
- Listing of AEs Leading to Discontinuation of Study Treatment

### 6.7.3. Laboratory Evaluations

Data for the following haematology, biochemistry, and urinalysis analytes received from central laboratory are to be measured at the scheduled visits indicated in the study flowchart.

**Table 9: Laboratory Tests**

| Haematology Test (SI unit) | Biochemistry Test (SI unit) | Urinalysis |
|---|---|---|
| • Red Blood Cell Count ($10^{12}$/L)<br>• Red Blood Cell Count indices:<br>  ○ Mean corpuscular volume (MCV) (fL)<br>  ○ Mean corpuscular haemoglobin (MCH) (fmol/cell)<br>  ○ Reticulocytes (%)<br>• Hemoglobin (g/L)<br>• Hematocrit (%)<br>• White Blood Cell Count ($10^9$/L)<br>• Differential WBC ($10^9$/L and %)<br>  ○ Neutrophils<br>  ○ Lymphocytes<br>  ○ Eosinophils<br>  ○ Basophils<br>  ○ Monocytes<br>• Platelet count ($10^9$/L) | • Alkaline phosphatase (ALP) (U/L)<br>• Alanine aminotransferase (ALT) (U/L)<br>• Aspartate aminotransferase (AST) (U/L)<br>• Total and direct bilirubin (umol/L)<br>• Total protein (g/L)<br>• Glucose (mmol/L)<br>• Creatinine (mmol/L)<br>• Blood Urea Nitrogen (mmol/L)<br>• Calcium (mmol/L)<br>• Potassium (mmol/L)<br>• Sodium (mmol/L)<br>• Troponin T (ng/mL)<br>• C-reactive protein (mg/L) | • Specific gravity<br>• pH<br>• Glucose<br>• Protein<br>• Blood<br>• Ketones<br>• Bilirubin<br>• Urobilinogen<br>• Nitrite<br>• Leukocyte esterase by dipstick<br>• Microscopic examination |

In accordance with the baseline value definition in Section 5.1.2, the absolute and percentage change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

Percentage change from baseline = [(post-baseline value– baseline value) / baseline value] × 100

All laboratory data will be reported in SI units. All quantitative laboratory test values at each assessed timepoints will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For summaries that present the worst value with respect to the reference range at the participant level, low and high are each chosen in preference to normal values. For parameters with both low and high reference ranges, participants who have assessments within both low and high ranges will be counted within each category for worst value summary tables.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory values will be assigned toxicity grades, when available, using criteria based on the NCI CTCAE version 5.0 scale (i.e. interventions and non-laboratory result checks will not be performed). For NCI CTCAE grades where bidirectionality is present (e.g. Hemoglobin, Lymphocytes, Calcium, Potassium and Sodium), the two toxicities will be assessed separately. (eg. for a sodium value of 158 mmol/L, this would be considered as grade 3 for hypernatremia. The same value would be assigned grade 0 for the analysis of hyponatremia.)

Parameters whose CTCAE grade can be derived are the following:

| Haematology Test | Biochemistry Test |
|---|---|
| • Absolute eosinophils (Eosinophilia)<br>• Hemoglobin (Anemia)<br>• Hemoglobin (Increased)<br>• Absolute lymphocytes (Decreased)<br>• Absolute lymphocytes (Increased)<br>• Absolute neutrophils (Decreased)<br>• Platelet count (Decreased)<br>• White blood cell count (Decreased)<br>• White blood cell count (Leukocytosis) | • Alkaline phosphotase (ALP) (Increased)<br>• Alanine aminotransferase (ALT) (Increased)<br>• Aspartate aminotransferase (AST) (Increased)<br>• Total Bilirubin (Increased)<br>• Calcium (Hypercalcemia)<br>• Calcium (Hypocalcemia)<br>• Creatinine (Increased)<br>• Glucose (Hypoglycemia)<br>• Potassium (Hyperkalemia)<br>• Potassium (Hypokalemia)<br>• Sodium (Hypernatremia)<br>• Sodium (Hyponatremia) |

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the Safety Analysis Set by treatment group and overall, as follows:

- Observed values and percentage change from baseline at each assessed timepoint for each standard continuous laboratory parameter.
- Number and percentage of subjects with categorized shift (low, normal and high) values relative to the reference range at baseline compared to each post-baseline timepoint for haematology and biochemistry.

- Number and percentage of subjects with worst categorized (low, normal and high) values relative to the reference range.

For haematology and biochemistry:

- Number and percentage of subjects with worst NCI-CTCAE toxicity values.
- Number and percentage of subjects with categorized shift NCI-CTCAE toxicity values at baseline compared to each post-baseline timepoint.

Listings of all clinical laboratory data including derived absolute change from baseline will be provided for the Safety Analysis Set. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low and NCI-CTCAE grading will be provided for applicable laboratory assessments.

### 6.7.4. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- pulse rate (bpm);
- respiration rate (breaths / min);
- body temperature (°C).

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

Vital sign values will be considered as potentially clinical important (PCI) if they meet criteria listed in Table 10.

**Table 10: Criteria for Potentially Clinically Important Vital Signs Parameters**

| Vital Sign | Criteria for observed value | Flag |
|---|---|---|
| Pulse Rate | <45 bpm | Low (L) |
| | ≥45 and <120 bpm | Normal |
| | ≥120 bpm | High (H) |
| | | |
| Systolic Blood Pressure (SBP) | <90 mmHg | Low (L) |
| | ≥90 and <160 mmHg | Normal |
| | ≥160 mmHg | High (H) |
| | | |
| Diastolic Blood Pressure (DBP) | <55 mmHg | Low (L) |
| | ≥55 and <100 mmHg | Normal |
| | ≥100 mmHg | High (H) |

The following will be summarized by treatment group and overall for the Safety Analysis Set:

- Observed values and absolute change from baseline at each assessed timepoint for each standard vital sign parameter using default summary statistics for continuous variables;
- The worst absolute change (most extreme value, either increase or decrease) for each variable for each participant will be summarized using default summary statistics for continuous variables.
- Any post-baseline PCI result for each variable.
- If participants have PCI assessments, both below and above PCI criteria (as indicated in Table 10), participants are counted in both categories for summary tables.

A listing of all vital signs data including derived absolute change from baseline will be provided for the Safety Analysis Set.

### 6.7.5. Electrocardiograms

Electrocardiogram (ECG) assessments will be taken during the study at screening, Days 1, 15, 29 (pre-dose), 43, 57 (pre-dose), 71 and 91. Assessments may be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression or in participants whose 2$^{nd}$ dose of MVA was delayed due to study pause. The following assessments are collected:

- An overall investigator assessment classified as normal, abnormal, not clinically significant / abnormal, clinically significant
- Heart rate (bpm);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia corrected QT (QTcF) interval (msec)

A summary table of absolute values and percentage change from baseline for ECG heart rate, PR interval, QRS interval, QT interval and QTcF interval will be presented over time for the Safety Analysis Set. A listing of all ECG data will be provided for the Safety Analysis Set.

### 6.7.6. Physical Examination

For each physical examination body system, the number and percentage of participant with abnormalities at baseline and at each assessed timepoint will be summarized by treatment group and overall for the Safety Analysis Set.

Physical examination findings (normal / abnormal) and details of abnormalities will be listed for each subject at each assessed timepoint.

### 6.7.7. Other Safety Variables

ECOG performance status will be listed for each subject at each assessed timepoint.

### 6.7.8. Interim Analysis and Data Monitoring

Apart from the data reviews performed by the Safety Monitoring Committee (SMC; detailed in the Safety Monitoring Plan), no interim analyses are planned for the Phase I part of the study..

## 6.8. Pharmacokinetic Assessments

Not Applicable.

### 6.8.1. Pharmacokinetic Analysis

Not Applicable.

## 7. Changes in the Conduct of the Study or Planned Analysis

The change from baseline for electrocardiograms have been added as a primary endpoint for the primary objective of evaluating the safety of VTP-850 prime-boost regimens.

# 8. Appendices

## Appendix 1: Document History

| Document Version, Status, Date | Summary / Reason for Changes |
|---|---|
| Version 1.0, Final, 31Oct2024 | Not applicable; the first version |

## 9. References

[1]ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at https://database.ich.org/sites/default/files/E9_Guideline.pdf

[2]ICH. *Addendum on Estimands and Sensitivity Analysis in Clinical Trials*, Guideline E9(R1). Available at
https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

[3]ICH. *Structure and Content of Clinical Study Reports*, Guideline E3, 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf

[4]*Common Terminology Criteria for Adverse Events (CTCAE) v6.0. Available at* https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60